

Oral presentation

SQUIRREL_{novo}: *de novo* design of a PPAR α agonist by bioisosteric replacement

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from 4th German Conference on Chemoinformatics
Goslar, Germany. 9–11 November 2008

Published: 5 June 2009

Chemistry Central Journal 2009, 3(Suppl 1):O4 doi:10.1186/1752-153X-3-S1-O4

This abstract is available from: <http://www.journal.chemistrycentral.com/content/3/S1/O4>

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Shape complementarity is a compulsory condition for molecular recognition [1]. In our 3D ligand-based virtual screening approach called SQUIRREL, we combine shape-based rigid body alignment [2] with fuzzy pharmacophore scoring [3]. Retrospective validation studies demonstrate the superiority of methods which combine both shape and pharmacophore information on the family of peroxisome proliferator-activated receptors (PPARs). We demonstrate the real-life applicability of SQUIRREL by a prospective virtual screening study, where a potent PPAR α agonist with an EC₅₀ of 44 nM and 100-fold selectivity against PPAR γ has been identified.

SQUIRREL molecular superposition is based on a graph-matching routine [4] and allows partial matching. We used this advantage for searching for bioisosteric replacement suggestions in a database of molecular fragments derived from a collection of drug-like compounds [5]. The bioisosteric groups suggested by our tool SQUIRREL_{novo}, can be used for ligand-based *de novo* design by a human expert. Using the fibrate derivative GW590735 [6] as query, we designed a novel lead structure by substitution of the acidic head group and hydrophobic tail. The synthesis and following testing in a cell-based reporter gene assay [7,8] revealed that the designed structure activates PPAR α with an EC₅₀ of 510 nM.

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